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DIABETIC NEPHROPATHY

A lncRNA and miRNA megacluster in diabetic nephropathy

Several microRNAs (miRNAs) have been implicated in the pathogenesis of diabetic nephropathy; however, a new report describes the discovery of a large megacluster of nearly 40 miRNAs hosted by a long noncoding RNA (lncRNA), which are co-ordinately upregulated in renal cells in response to diabetic stimuli. "We found that the target genes of several miRNAs within this cluster had functions related to diabetic nephropathy and that the host lncRNA, lnc-MGC, was regulated by an endoplasmic reticulum (ER) stress-related transcription factor called CHOP," explains researcher Rama Natarajan. "Moreover, targeting lnc-MGC inhibited the expression of not only the host lnc-MGC, but also key cluster miRNAs in the kidney, and prevented features of early diabetic nephropathy. Given the emerging interest in lncRNAs and their potential roles in disease states, our observations are timely and clinically relevant."

To identify coding and noncoding transcripts upregulated in the glomeruli of mice with streptozotocin-induced diabetes, Natarajan and colleagues used next-generation sequencing, which led to the identification of the miRNA megacluster and lnc-MGC. Levels of the miRNAs and lnc-MGC were also upregulated in cultured mouse mesangial cells in response to the diabetogenic stimuli TGF-β1 and glucose, and many of the cluster miRNAs were present in glomeruli of patients with diabetic kidney disease. The target genes of several cluster miRNAs were identified as regulators of various pathways relevant to the pathogenesis of diabetic nephropathy, including TGF-β signalling, cellular hypertrophy, extracellular matrix synthesis and ER stress. ER stress was also identified as a regulator of the megacluster, as knockdown of *Chop* with small interfering RNA decreased the expression of lnc-MGC and key cluster miRNAs, and features of diabetic nephropathy were attenuated in *Chop*-knockout mice with streptozotocin-induced diabetes.

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Philip Patenall/NPG

To assess the function of lnc-MGC and the miRNA cluster in vivo, the researchers designed GapmeRs to inhibit the expression of lnc-MGC. "GapmeRs are antisense oligonucleotides that are modified by locked nucleic acids and phosphorothioates to increase affinity to the target RNAs," explains Natarajan. "They act by making DNA–RNA hetero-duplexes, which trigger RNase H-mediated target degradation. Importantly, GapmeRs have not been previously tested to target lncRNAs in the diabetic kidney." Injection of diabetic mice with the GapmeR inhibited not only the expression of lnc-MGC, but also candidate cluster miRNAs, and reduced expression of profibrotic genes and histologic features of early diabetic nephropathy.

The researchers are planning further studies to examine the functions of the cluster miRNAs. "We will perform detailed *in vitro* mechanistic studies to assess the mechanisms by which the miRNAs and host lncRNA are regulated and how they promote ER stress, fibrosis and hypertrophy," says Natarajan. They also believe that their findings have implications for the development of noninvasive clinical biomarkers of early stage diabetic nephropathy or novel therapies to target the corresponding human noncoding RNAs. "In the future, we hope that treatment of diabetic patients with GapmeRs targeting human lnc-MGC would prevent the progression of diabetic nephropathy and other diabetes-related complications."

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ORIGINAL ARTICLE Kato, M. *et al.* An endoplasmic reticulum stress-regulated lncRNA hosting a microRNA megacluster induces early features of diabetic nephropathy. *Nat. Commun.* http://dx.doi.org/10.1038/ncomms12864 (2016)
FURTHER READING Lorenzen, J. M & Thum, T. Long noncoding RNAs in kidney and cardiovascular diseases. *Nat. Rev. Nephrol.* 12, 360–373 (2016).